National Research Council Canada
Conseil national de recherches Canada

Corporate Services
Service intégrés

Ottawa, Canada
K1A 0R6

NRC · CNRC

RECEIVED
CENTRAL FAX CENTER
SEP 0 2 2004

FACSIMILE COVER SHEET

OFFICIAL

DATE: September 2, 2004 Our File No. 11054-1

ADDRESSEE/ U.S.P.T.O.

FAX NO./ (703) 872-9306

SENDER/ Margaret McKay, IPS FAX NO./(613) 952-6082

NO. OF PAGES (INCLUDING COVERING PAGE)/ (15)
NOMBRE DE PAGES (Y COMPRIS LA PAGE COUVERTURE):

PLEASE CALL US AT 613 990-3648 IF THE TRANSMITTAL IS INCOMPLETE.
VEUILLEZ NOUS REJOINDRE AU 613 990-3648 SI CE N'EST PAS COMPLET.

COMMENTS/COMMENTAIRES:

SEE ATTACHED

Canada

BEST AVAILABLE COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Applicant(s):	Saran A. Narang et al
Serial No:	10/031,874 Filing Date: November 14, 2002
Examiner:	David J. Blanchard Art Unit: 1642
Title:	Single-Domain Antigen-Binding Antibody Fragments Derived from Llama Antibodies
Docket No:	11054-1

September 2, 2004

OFFICIAL

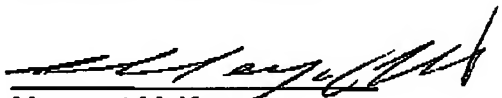
To: The Commissioner of Patents
and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450
U.S.A.

Sir:

This is in Response to the Official Action of June 2, 2004.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment.

Respectfully submitted,

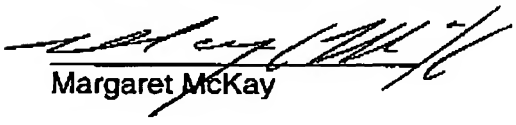


Margaret McKay
Patent Agent for Applicant
Regn No: 52,519

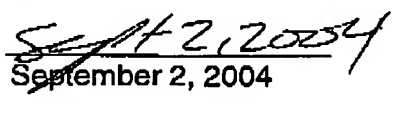
:sta
Tel: 613-991-6853

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.



Margaret McKay



September 2, 2004

IN THE DESCRIPTION

Kindly substitute enclosed amended description page 12 for description page 12, currently on file.

As is well known to those skilled in the art, the probability of isolating a protein with high affinity or specificity against a target (antibody) of interest increases with the size of the library. Generally, two different types of vectors are used for generating phage display libraries: phagemid vectors and phage vectors. Libraries having size in the order of 10^8 can be constructed with relative ease using phagemid vectors. However, a phagemid-based libraries suffers from some serious drawbacks. First, phagemid vectors provide typically a monovalent display and therefore may not select for lower binding (of lower affinity), but potentially important antibody fragments. Second, a phagemid-based library allows for the enrichment of phage particles displaying deleted versions of the antibody fragments. Such particles, often with no binding activity, are preferably selected during the panning process over those displaying the full-length fragments and therefore obscure the process of selection of the full-length binders. Third, constructing a phagemid-based library requires a helper phage and therefore library construction, panning and downstream phage binding assays become a far more complicated and tedious task. For these reasons the use a phage vector for the library construction is preferred.

One of the most widely used phage vectors is fd-tet (Zacher III et al., *Gene*, **9**, 127-140 (1980)) which consists of fd-phage genome, plus a segment of Tn10 inserted near the phage genome origin of replication. Tn10 contains a tetracycline resistance gene, tetA, and thus confers tetracycline resistance to the host cells carrying the fd-tet vector. It has often been observed that the size of the fd-tet based library was generally low (in the range of $10^5 - 10^6$) (Harrison et al., Methods in Enzymology [Ed. Abelson, J.N.], **267**, 83-109 (1996); Krebber et al., *FEBS Letters*, **377**, ~~277-331~~ 227-231 (1995)), possibly due to the toxic effect of tetA gene product on the host cells. According to the modified procedure of the present invention, the library was propagated as plaques in the absence of tetracycline, resulting in a llama V_HH library of size of approximately $8.8x10^8$. This is the largest size library ever obtained using fd-tet vector. Due to its size, the library has an enhanced probability of selecting therefrom proteins (antibody fragments) binding to almost any given target (antigen).